

*The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided. The patient described in this column is a composite with characteristics of several real patients.*

### Dispensary cannabidiol marijuana and first-episode mania

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A 29-year-old man was admitted to hospital with a first episode of mania with no past or family psychiatric history. He was brought to the emergency department after an abrupt change in behaviour of 1-month duration. Symptoms included decreased sleep, profoundly pressured speech, racing thoughts, distractibility, lability, irritability, grandiosity, paranoia and delusions of reference. His previous use of cannabis was minimal until 10 months prior, when a cannabis dispensary opened up on his route home from work. He obtained a medical marijuana prescription online and started purchasing product. He used no other drugs. Initially, he smoked cannabis weekly, but in the month before his episode he was let go from his job and increased to daily use, experiencing a change in his mood and thinking immediately thereafter. There may have been subclinical mood elevation for several months before his acute episode. Of note, he used high-cannabidiol (CBD) marijuana strains, and ostensibly very little tetrahydrocannabinol (THC).

The initial diagnosis was drug-induced mania, which was treated with 1 mg/d of risperidone. As the patient was admitted to hospital, he stopped smoking cannabis immediately and did not restart cannabis at any time during the treatment period. After several days, there was no change in symptoms, and his Young Mania Rating Scale (YMRS) score was 39. He was titrated up to 4 mg with little improvement in symptoms (YMRS score of 36 at 3 weeks). Ultimately, lithium was started with little effect at an initial dose of 600 mg twice daily

(blood level 0.68 mEq/L). The dose was increased at weekly intervals, and upon reaching 900 mg in the morning and 1200 mg before bed (blood level 1.32 mEq/L), his mania started improving. One week thereafter, his YMRS score improved to 19, and then it improved to 4 at 3 weeks. The dose was decreased to 900 mg twice daily, and his blood level dropped to 1.02 mEq/L with no return of symptoms, leading to discharge.

Clinicians have associated cannabis with psychotomimetic properties owing to compelling evidence of a dose-response relationship between cannabis use and psychosis.<sup>1</sup> These psychotomimetic properties are largely due to the effects of  $\Delta$ -9-tetrahydrocannabinol, 1 of approximately 60 cannabinoids in marijuana.<sup>2</sup> Although evidence in bipolar disorder is less robust than in psychosis, there is an association between cannabis use in bipolar disorder and younger age of onset, poorer medication adherence, a more severe course of illness, a higher number of manic or depressive episodes and a greater degree of dysphoria versus euphoria (for a review, see Aubry<sup>3</sup>). Recent research has explored therapeutic benefits of endocannabinoid manipulation and use of CBD, the main nonpsychotropic component of the *Cannabis sativa* plant.<sup>4</sup> A Dutch study of 1877 participants determined a small but significant inverse association between CBD content and self-reported positive symptoms, but not with negative symptoms or depression.<sup>5</sup> The authors suggested that the small effect size might be due to the dosage of CBD in cannabis products intended for smoking being much lower than in the purified oral form, and the therapeutic properties of CBD are further reduced by the burning process when cannabis is smoked.<sup>5</sup> Evidence has supported potential therapeutic benefits of CBD in neurologic conditions such as epilepsy.<sup>6</sup> In

psychiatry, some evidence supports CBD use in the domains of anxiety,<sup>7</sup> psychosis<sup>8</sup> and opioid use.<sup>9</sup> Early evidence is promising, but more randomized, quality-controlled studies are required.

This patient purposefully chose to use CBD products. Nonetheless, he had serious psychiatric sequelae, which were temporally linked with cannabis use but did not improve with cessation. The reason is unclear, but there are several possibilities. This could have been an index manic and psychotic episode unconnected to the patient's drug use, although with no previous symptoms and a slightly older age of onset. Or, his mania could have resulted from one of the many other cannabinoids in marijuana. Alternatively, CBD use may have resulted in his symptoms, representing an atypical reaction to CBD. Finally, although he believed he was using the "medicinal" cannabis component of CBD, he may have elevated THC exposure, or combustion/smoking-associated CBD attenuation, resulting in his hospitalization. A study of cannabinoid concentrations in Health Canada-regulated medical cannabis demonstrated a preponderance of THC-dominant strains, the majority with "potent" THC levels.<sup>10</sup> In the absence of component-specific drug testing, we cannot definitively determine the etiology, and the natural history of his illness moving forward may provide insight. Thus, notwithstanding the labelling of cannabis for "medicinal" use with high CBD, clinicians should be extremely cautious for psychiatric sequelae and not take for granted that the type of cannabis consumed is safe or consistent with its labelling, especially when smoked. Further, patients should be provided reliably sourced educational materials on cannabis to ensure they are aware of risks and benefits; this may be an important part of relapse prevention.

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